SOME ASPECTS OF CARBOHYDRATE METABOLISM

JOHN R. MURLIN,
Director of the Department of Vital Economics, University of Rochester, Rochester, N. Y.

An eminent biochemist was wont to say facetiously that he had the ambition to make a lump of sugar and to lay an egg. He lived to fulfill the first of these aspirations, but died before he had the egg quite finished. I refer, of course, to Emil Fischer. He made not only one but several kinds of sugar and together with Kossel, about the beginning of this century, he revealed the fundamental nature of proteins. In carbohydrate metabolism one cannot omit the proteins, for carbohydrate can be formed from protein and this is an important source of biotic energy. Some reference will be made to this aspect of carbohydrate metabolism, but I shall be concerned mainly with the question of the possible formation of sugar from the other principal source of energy, namely, fat.

Metabolism properly begins with digestion. Let us look just a moment at the nature of this change and particularly its rate. The nature of the change is indicated by the reaction $(C_6H_{10}O_5)n + nH_2O \rightarrow (C_6H_{12}O_6)n$. This is called hydrolytic cleavage. All of the ordinary processes of digestion are of this nature.

Digestion of starch is begun by saliva in the mouth, provided the saliva is well mixed with the food. A familiar laboratory experiment to illustrate the rapidity of the action of ptyalin, the starch splitting ferment of the saliva, is to chew a soda biscuit or cracker for two minutes, place the chewed mass over a filter paper and wash with distilled water. Applying a copper reduction test to the filtrate one gets a good reaction for sugar.

Further evidence of the rapid action of saliva is obtained by digesting in glassware cooked cereal breakfast foods. The following Table (I) illustrates:

TABLE I.

DIGESTION FOR FIVE MINUTES AFTER COOKING FIFTEEN MINUTES.

	Complete Digestion.	Digestion to Solubility.
	%	%
Wheat endosperm	22.7	70.7
Precooked oats	34.9	77.2
"Whole wheat"	26.8	67.6
"Toasted whole wheat"	31.1	66.8

Biedermann speaks of the almost "explosive action" of ptyalin in digestion of starch. If the starch be already soluble the digestion to sugar is even more rapid.

Cannon at Harvard showed about 30 years ago that digestion of starch can proceed in the stomach after a mixed meal for from 15 to 90 minutes, being stopped only when the entire stomach contents become acid. This has been confirmed by Bergeim and Hawk, who used the retention tube and drew up samples of stomach contents at various intervals after digestion started. Under favorable circumstances therefore the starch may be digested to complete solubility therefore in the stomach. Disacchrides like cane sugar need only to be inverted, i. e., split into two molecules, for single sugars to be ready for absorption—

$$C_{12}H_{22}O_4 + H_2O \rightarrow 2C_6H_{12}O_2.$$

Lusk (2) in 1898 proved that this takes place rapidly in the stomach under the influence of the HCl of the gastric juice.

When the food leaves the stomach, therefore, the carbohydrate is already pretty well digested. The process is continued speedily by the amylase of the pancreatic juice, which would suffice of itself to complete the whole series of changes, if no other enzyme were available.

We have been interested in our laboratory in the enzymes of the intestinal juice produced by the mucosa of the intestine. We have already proved that a piece of intestine transplanted (3) into the abdominal wall under the skin secretes a greater quantity of juice when the dog eats, even when there is no connection by blood vessels or nerves with the rest of the alimentary tract. Incidentally, this proves hormone control of this secretion. Two of the enzymes which have been studied are an intestinal amylase and a sucrase. The action is feeble compared with the enzyme of the pancreas, nevertheless they are sufficient to completely split several grams of starch and cane sugar in the course of 24 hours.

CARBOHYDRATE IN THE BLOOD.

It is clear then that we are specially equipped with a very efficient series of chemical agents to digest carbohydrates speedily—far more speedily than either fats or proteins can be digested. When digestion is complete, the starch is all reduced to glucose and the several disaccharides have been reduced to monosaccharides. Those which are not glucose, like fructose

and galactose, get transformed into glucose either in the course of absorption or in the liver, so that all the carbohydrate is glucose by the time it reaches the general circulation for distribution to all the tissues.

This sugar of the blood may be formed also from protein as was first proved by Cl. Bernard, the great French physiologist, who flourished about the middle of the last century. He was following the fate of foodstuffs which disappeared from the alimentary tract and had reached the point of investigating what happens in the liver which, you remember, receives all the blood coming from the alimentary organs through the so-called portal system. Taking blood as it entered the liver by the portal and comparing it with blood as it leaves the hepatic vein, Bernard found that when a dog had been fed a large amount of meat the liver gave up far more sugar than it received without any change in the amount retained. This could only mean that carbohydrate is formed from protein. We know now that the reaction fundamentally is as follows:

$$CH_3 \cdot CH\ HN_2 \cdot COOH + H_2O = CH_3 \cdot CHOH \cdot COOH + NH_3$$
$$2\ CH_3 \cdot CHOH \cdot COOH = C_6H_{12}O_6.$$

Alanin, a 3-carbon amino acid typical of the building stones in protein is hydrolyzed to lactic acid and from two molecules of this one of glucose can be formed. Another possible reaction is by oxidation of pyruvic acid and by reduction to glucose.

We have then at least two sources of the sugar in the blood—the carbohydrate of the food and the protein not needed for growth or repair of the tissues. The capacity of the body to handle sugar may be determined by what is called a tolerance test. Injecting a known amount of glucose at a certain rate into a vein it very quickly mixes with the whole blood and the level of blood sugar found in any vein plotted against time gives a tolerance curve. If the curve falls promptly tolerance is good; if it falls slowly, tolerance is poor. A few curves obtained on (4) normal and diabetic dogs are given later (p. 349).

The whole picture of sugar regulation in the blood is nicely illustrated by a diagram designed by Drs. Ringer and Baumann (5) for their article in Endocrinology and Metabolism, published in 1922. It shows the ways in and the ways out, and the different organs which participate in maintaining the blood sugar at an average normal level. This chart, however, requires a little modification now to express what has been learned regarding the action of insulin and epinephrin.

METABOLISM OF CARBOHYDRATE.

There are three ways in which sugar of the blood may be disposed of normally. It may be oxidized at once to yield physiological energy and heat; it may be converted to glycogen for temporary storage—a checking account in the bank; or it may be converted to fat—a savings account or permanent investment. The chief tissue for oxidation is muscle, although practically every other tissue, so far as they have been studied, can also oxidize sugar. This universal capacity to burn this foodstuff has lead some authors, rather hastily as it seems to me, to conclude that sugar is the only fuel of life. This conception received great encouragement a few years ago by the development of the so-called Hill-Meyerhof theory of muscular contraction and recovery. Hill (6) found that when a frog's muscle contracts in oxygen it gives off a little heat during the contraction phase, but gives off much more during recovery after the contraction and relaxation have passed. When the muscle contracts in nitrogen, only the first or "initial" heat is produced, the delayed or recovery heat is wholly lacking. It happens that this fits in perfectly with observations previously made by Fletcher and Hopkins that when a muscle contracts it produces lactic acid, the lactic acid disappearing rapidly if oxygen is supplied, but not disappearing if the muscle is bathed by nitrogen gas. Hill inferred that it was the cleavage of some carbohydrate into lactic acid which produced the initial heat and the oxidation of lactic acid which produced the heat of recovery. Meyerhof (7) working on the same subject by biochemical methods came to the conclusion that the only carbohydrate which can fit the requirements is glycogen, which is a normal constituent of all muscle. He agreed with Hill that the cleavage produces lactic acid, and in fact that the yield of heat which Hill found is just the theoretical heat which should appear when glycogen is broken down to lactic acid, plus the amount used in deionizing the protein combined in solution with alkali and making of it a lactate salt. Meyerhof's equation for the process was as follows:

$$5/n\ (C_6H_{10}O_5) + 5H_2O \rightarrow 5C_6H_{12}O_6 \rightarrow 1C_6H_{12}O_6 + 8\ C_3H_6O_3 \text{ (naerobic phase)}$$

$$1C_6H_{12}O_6 + 8C_3H_6O_3 + 6\ O_2 \rightarrow 6\ CO_2 + 6H_2O + 4C_6H_{12}O_6 \rightarrow 6CO_2 + 10H_2O + 4/n\ (C_6H_{10}O_5). \quad \text{R. Q.} = 1.0$$

(oxidative phase)

The second part—the oxidative phase—describes what happens when plenty of oxygen is present. You will observe that we start with 5 molecules of glycogen and end up with 4. Differently expressed, we start with 30 carbons as glycogen and at the end of the first reaction we have 30, 6 of them as glucose and 24 as lactic acid. In the second reaction the glucose gets oxidized and the 24 carbons of lactic acid (8 molecules) get resynthesized again to glycogen. In Meyerhof's conception the oxidation of lactic acid is for the purpose of restoring the potential energy of glycogen just as if a spring were being wound up or, still better, as if a battery were being recharged ready to deliver its energy again when the switch is thrown, i. e., when the muscle gets a stimulus from a nerve. In his original statement Meyerhof implied clearly that only carbohydrate could be oxidized to furnish the energy for synthesis. Later he disclaimed any intention of excluding fat as a source of this energy.

However, this beautiful conception has in the last six years been considerably defaced. You will observe that the star performer in that view is lactic acid. What Hill (8) calls the "revolution in muscle physiology" which broke out on the last day of 1926, brings forward an entirely new star performer which is called "phosphagen," a compound of creatin and phosphoric acid. It turns out on Hill's own confession that he and Meyerhoff had compromised a small error in their results for the sake of the major conception and in the hope that future work would clear up the discrepancy. The Eggletons (9) in England described phosphagen and almost simultaneously Fiske and Subarrow (10) at Harvard described the same compound as phosphocreatine, showing that it is a very labile substance yielding equivalent proportions of creatine and phosphoric. The Eggletons showed further that this substance is broken down when muscle contracts and disappears again when oxygen is admitted. Hill's own work with Hartree had revealed that there is a small amount of the delayed heat not accounted for by the oxidation of lactic acid and Embden and co-workers proved that some lactic acid appears after contraction is over. These facts did not fit into the nicely balanced thermodynamic equation of Hill and Meyerhof. There were several other facts which we shall not have time to enumerate that were not easily reconciled with the theory. The final blow came, however, with the accidental discovery by Lunds-

gaard (11) at Copenhagen in 1930 that muscle poisoned with iodoacetic acid contracts without producing any lactic acid. This has now been fully confirmed many times and the new theory, which must take Lundsgaard's name, includes phosphagen as follows: When a muscle contracts phosphagen breaks down into creatine and phosphoric acid. Fischer and Meyerhof (12) and Lundsgaard (13) independently have shown that this furnishes the energy for contraction. The energy for resynthesizing the phosphagen in turn comes in part from the cleavage of glycogen to lactic acid, which explains why lactic acid appears after contraction, and the energy for rebuilding the glycogen comes from combustion of *lactic acid or glucose*, or, as many now believe, from fat if carbohydrate is not present in sufficient quantity. Thus we see how carbohydrate is disposed of in muscular work. Every contraction, however small, takes place by the release of potential energy from a complex compound when it suddenly explodes, so to speak, into smaller fragments. But the mechanism is automatic. No sooner is this compound exploded, than the fragments are gathered together and resynthesized in part, by expenditure of energy from another explosion—this time of glycogen, a complex carbohydrate. The second explosion is unexploded, if I may coin the word, by combustion of other carbohydrate and lactic acid, a degenerate form of sugar, becomes ennobled, so to speak, as it continuously returns to the higher form. Lohmann (14) recently has shown that the formation of lactic acid from glycogen in dialyzed muscle extract requires the action of a co-ferment system consisting of inorganic phosphate, adenyl-pyrophosphate and magnesium. Presumably this system is operative also in the live muscle.

Lactic acid, we know now, can be formed in all kinds of tissues, which leads us to suppose that much the same mechanism for release of energy exists in all. But it does not appear in more than trifling amounts *unless oxygen is lacking.* Any form of asphyxia whether local or general always reveals it in larger amount. When a muscle works faster than the physiological rate, which means faster than oxygen can be supplied to resynthesize the lactic acid, it becomes fatigued, as we all know. Washing away or oxidizing away the lactic acid relieves fatigue.

THE RESPIRATORY QUOTIENT.

Dr. Carpenter has already explained to you what the respiratory quotient signifies. This relationship of the volume of CO_2 eliminated to the volume of O_2 absorbed varies ordinarily only between about 0.73 to 1.00. The lower figure means combustion of nearly pure fat, the higher of nearly pure carbohydrate. These facts follow from the following simple equations:

Tripalmitine is $C_3H_5(C_{16}H_{31}O_2)_3$ or

$$C_{51}H_{98}O_6 + 72.5\ O_2 = 51\ CO_2 + 49\ H_2O$$

$$\frac{51\ CO_2}{72.5\ O_2} = 0.703$$

Glucose

$C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O$. Hence $\frac{6\ CO_2}{6\ O_2} = 1.0$.

It is relatively simple to obtain respiratory quotients on the entire body, and Dr. Carpenter has explained to you the method. Having found the non-protein R. Q., then, for any quotient intermediate between 0.707 and 1.0 we can by a relatively simple calculation find the percentage of the total oxygen taken up by the oxidation of each of the two non-nitrogenous food stuffs. Thus $100\ \frac{\text{R. Q.} - 0.707}{0.293}$ gives the percentage of carbohydrate oxygen; $100\ \frac{1.00 - \text{R. Q.}}{0.293}$ gives the percentage of oxygen for fat.

If we eat large amounts of carbohydrate we are sure to obtain R. Q.'s close to 1.0 and if we continue on such diets for a few days we get R. Q.'s higher than 1.0, which mean that carbohydrate is being converted to fat, thus:

$$4\ C_6H_{12}O_6 + O_2 = C_{16}H_{32}O_2 + 8\ CO_2 + 8H_2O.\ \frac{8\ CO_2}{1\ O_2} = 8.0\ \text{R.Q.}$$

glucose palmitic acid

The R. Q. of this reaction would be 8.0, but of course only a little carbohydrate can be converted to fat at a time, and the consequence is a little of this reaction would be mixed with much of the ordinary metabolism with a quotient say of 0.90.

Suppose 2 per cent of the metabolism represented a R. Q. of 8.0 and 98 per cent represented an R. Q. of 0.90, and suppose the total oxygen absorbed was 10 L. Taking 0.2L of O_2 at an R. Q. of 8.0 the CO_2 would be 1.6 L, and the total CO_2 would be 8.82 + 1.6 = 10.42. Since the O_2 we have supposed is 10 L, the total R. Q. would be 1.04. The highest R. Q.'s ever obtained were about 1.5–1.6 which at the same rate of O_2 absorption we have imagined would mean the use of approximately 10 per cent of the oxygen for the conversion to fat, with a R. Q. of 8.0 and 90 per cent for ordinary metabolism with the R. Q. of 0.90.

The inverse relationship holds if we have conversion of fat to carbohydrate. This is a hotly controverted question at present and we shall encounter some new evidence in the latter part of this lecture. Suppose palmatic acid were converted over to glucose by Bleibtrau's reaction, what would be the R. Q.?

$$3\ (C_{16}H_{32}O_2) + 21\ O_2 = 8\ (C_6H_{12}O_6)$$

There is no R. Q. of this reaction because no CO_2 is produced. What the effect on the total R. Q. would be could only be determined by knowing how much sugar was being formed. Let us suppose that we could demonstrate the production of 10 gm. sugar in a period in which 8 L of CO_2 were being eliminated and the basal R. Q. was 0.8, i. e., 10 L of O_2 were absorbed. Imposing the special conditions which produce 10 grams sugar the extra oxygen necessary is found by the proportion

$$\begin{array}{rrrrr} 8\ (C_6H_{12}O_6) & : & 21\ O_2 & : : & 10\ \text{gm.} : x \\ 1440 & : & 672 & : : & 10\ \text{gm.} : 4.66\ \text{gm.} \end{array}$$

This gives the O_2 in grams. Multiplying by 0.7 (actually 0.6998) we get 3.26 liters. Adding this to 10 gives 13.26 liters and dividing into 8 L CO_2 we arrive at the R. Q. 0.60. Properly obtained quotients in this neighborhood can mean nothing else than the formation in metabolism of oxygen-rich substances (carbohydrates) from oxygen-poor substances (fats).

REGULATION OF CARBOHYDRATE METABOLISM.

In 1889 Minkowski working at Königsberg in East Prussia, observed that a dog whose pancreas had been removed excreted large amounts of sugar. This was the first step toward solution of the extremely important medical problem of diabetes mellitus. There had been many indications that the pancreas, if not the actual site of the disease, at least was involved. For example,

autopsies frequently had revealed that the pancreas was very much shrunken in the last stages of diabetes. There had also been indications of degenerative processes visible under the microscope. Minkowski himself undertook to demonstrate that the pancreas contains an extractable substance which can take the place of the pancreas itself in the regulation of carbohydrate metabolism, for it was just at this time, as Minkowski was continuing his work on pancreatectomy and its effects on metabolism, that Murray in England was demonstrating that an extract of thyroid gland can replace the gland itself in restoring a myxodematous person to normal. Minkowski did not succeed in this attempt for reasons which now are perfectly clear. But he did formulate perfectly definite ideas as to the role played by the pancreas in carbohydrate metabolism. He stated that the reason sugar appears in the urine when the pancreas is removed or when seriously diseased, is that sugar cannot be oxidized. Something produced by the pancreas participates in the oxidation of sugar. When that substance is lacking, oxidation fails, sugar piles up in the blood, and leaks out through the kidney. The name "hormone" for such a material had not yet been invented, but of course now we apply the term hormone to such a product continuously formed by an organ, and delivered directly to the blood stream.

Several observers have now demonstrated that the general seat of the metabolic action of insulin, so far as combustion is concerned, is in the muscles. Taking blood from the arteries supplying the muscles and from the vein draining the blood away, before and after introducing insulin, shows clearly that the difference in sugar concentration between these two bloods increases when insulin reaches the muscle. A second important action, probably not less important than the combusion of sugar, is its prompt conversion to glycogen when excess exists in the blood. This process also is facilitated by the presence of insulin as has been demonstrated clearly by Cori and Cori (15).

As early as 1907 it was surmised by Zuelzer that the internal secretion of the pancreas, which regulates sugar metabolism, is antagonized by epinephrin, the secretion of the adrenal gland. Zuelzer (16) actually had a pancreas preparation which would diminish the excretion of sugar of a diabetic dog and would lower the blood sugar previously raised by the injection of epinephrin. This antagonism between insulin and epinephrin is now well established. When epinephrin is injected into a

normal animal the blood sugar rises because glycogen in the liver is converted into glucose rapidly and passes out into the blood stream. Epinephrin even reduces the combustion of sugar (17). When insulin is given exactly the opposite effects are seen. Blood sugar is reduced by two methods, combustion in the muscles and storage of glycogen particularly in the liver. It has been suggested that an excess production of epinephrin, even though small in amount, continuing over a period of years, might possibly be the cause of diabetes mellitus. Insulin, according to this idea, would be continuously suppressed in its action and eventually stopped altogether. Epinephrin would account for the high blood sugar and the inability of the diabetic organism to oxidize sugar or to form glycogen. This remains only a working hypothesis.

A rival theory to that of Minkowski, originally conceived by vanNoorden in Vienna, is that in the absence of the pancreatic hormone, sugar is produced in excessive quantity by the liver and piles up in the blood, not because it cannot be burned, but merely because more is produced than is required in the muscles and elsewhere. Insulin then would have as its primary function the inhibition of sugar formation. This so-called over-production theory has some few facts in its favor. But the discovery of insulin has tended to confirm Minkowski's idea that the primary function of insulin is oxidation rather than the suppression of sugar formation.

For example, a dog made completely diabetic by extirpation of the pancreas has an R. Q. close to the theoretical for the combustion of fat, namely, 0.7. Quite frequently the quotient falls somewhat below this, indicating, according to one interpretation that fat is being converted to sugar and according to another interpretation that fat is only partially oxidized, the products instead of being excreted through the lung being excreted through the kidney. These products are the so-called acetone bodies, diacetic acid, acetone itself and β-hydroxybutyric acid. I shall not have time to go into the chemistry of these ketones, so called, but will indicate merely that if these partially oxidized products are formed in large quantity, there is no doubt that the result would be a depression of the R. Q. Magnus-Levy has concluded that a normal subject producing 40 grams of Beta-hydroxybutyric acid would have an R. Q. in the neighborhood of 0.68. Giving insulin invariably increases the respiratory quotient, provided glucose is available.

GLUCONEOGENESIS.

I shall devote the remainder of my time to a discussion of the processes described by this term, which means the new formation of sugar from either protein or fat. The term was introduced by the vanNoorden school to account for the excess production of sugar from other than carbohydrate sources. It has been revived and discussed energetically by Macleod and his pupils at Toronto and latterly at Aberdeen. There are three main lines of investigation of this subject: (1) The D:N ratio in the urine of diabetic subjects; (2) Perfusion experiments, chiefly perfusions of the liver; (3) Respiratory metabolism.

The D:N ratio is the relationship of dextrose in the urine of a diabetic animal to the nitrogen excreted. The argument as regards the new formation of sugar will appear in a moment. We have three well studied types of diabetes: (1) the human subject, seriously ill because of degeneration of the pancreas; (2) the animal, chiefly the dog, after removal of the pancreas; and (3) the animal poisoned with the glucoside phlorhizin. In all three of these types of diabetes sugar which cannot be oxidized appears in the urine. When there is no carbohydrate whatsoever in the food the carbohydrate of the body itself is quickly exhausted and nevertheless sugar continues to be excreted. Obviously it must come from some other source than carbohydrate. Now if the excess sugar bears a definite ratio to the nitrogen of the urine, since nitrogen can come only from the protein, it will be safe to infer that the sugar also comes only from the protein. The facts are that the D:N ratio is a reasonably fixed quantity in the phlorhizinized animal, as Graham Lusk was the first to prove definitely. Lusk's ratio, 3.65 to 1, has become a pilot light in the study of diabetes. It means that a dog, under the influence of phlorhizin for about three days, fed meat or meat and fat, will continue to produce sugar in relation to N of the urine in such a proportion that 100 grams of protein is forming approximately 58 grams of sugar. Incidentally, this fact illustrates the extreme difficulty in which the totally diabetic person found himself before the discovery of insulin. He lost through the urine all of the carbohydrate eaten, nearly 60 per cent of his protein, and could very imperfectly metabolize fat. In the depancreatized dog the average D:N ratio beginning about two days after the pancreas was removed, and continuing as long as the dog could

eat a meat or meat and fat diet was, as Minkowski found, about 2.8 to 1. This ratio ever since has been called the Minkowski ratio. It means that approximately 44.8 grams of sugar can come from 100 grams of protein in the depancreatized dog. In our experience, however, the Minkowski ratio is much more difficult to establish than is Lusk's ratio on the phlorhizinized dog. After all, it is only an average ratio of some nine dogs as studied in Minkowski's laboratory and fed exclusively on meat. Ratios ranging between 2.6 and 1.0 are not at all uncommon, when the appetite fails, as frequently happens in the later stages of insulin deficiency. However, the interesting point in this particular connection is that the ratio under meat feeding rarely goes higher than, say, 3.0.

In human diabetes one is met by the difficulty that the patient is not always reliable. You can not control your experiment so well as you can with an animal. You cannot lock up a diabetic patient in a cage and have the cage locked in a room and see that the patient gets only certain items of food and that no urine is lost. As a consequence, ratios have been much more variable in human diabetes than in animal experimentation.

If all of the carbon of protein were converted to sugar, the D:N ratio would lie from 6.4 to 6.7, depending upon the exact composition of the protein fed. To prove beyond a doubt the conversion of fat to carbohydrate, it is conceded by the believers in gluconeogenesis from fat that the ratio must be higher than 6.7 to 1. Such ratios have been reliably reported in clinical studies of human diabetes, but it must be said that in the most carefully controlled work, as, for example, in Woodyatt's laboratory in Chicago, in Wilder's laboratory at the Mayo Clinic and in Joslin's laboratory in Boston, such ratios are very infrequently found. Likewise ratios of this order are never found in properly controlled work on diabetic animals. Therefore the evidence from the study of the D:N ratio is that sugar cannot be formed from fat. The fundamental economy underlying this fact seems to be the following: Nature is a better banker than man. Whenever we have an income of energy greater than our expense requirements, the balance is put into savings. Normally we have a checking account which we call glycogen and we have a more permanent savings account which we call fat. Now it is obviously in the interest of good physiological economy, as it is in the interest of good

financial economy, to conserve the more fixed savings. It should be, and it is easier to convert a favorable balance into savings than to convert permanent savings back into small change for current expense account. In primitive man this physiological principle had survival value, for when food was abundant the surplus energy could be stored away in his body as fat and could be drawn upon with difficulty only, inducing him thereby to seek other sources of food before the reserve had been exhausted. This principle is by no means so important for modern man with food everywhere abundant. It is rather an embarrassment because we find it all too easy to put food into the reserve account and all too difficult to take it out again.

The second line of evidence in this study of gluconeogenesis comes from the perfusion of the liver. This is a very common type of physiological experiment. Much information has been gained regarding the intermediary stages of the metabolism of protein and carbohydrate and to a less extent of fat by setting up an apparatus by which defibrinated blood can be pumped through the blood vessels of the liver over and over again, the liver meantime being kept at body temperature in a water bath and as nearly normal as we can imitate normal conditions outside the body. For example, it was long ago discovered that lactic acid in the perfused liver could be converted to sugar and also to glycogen. This supplements the fundamental muscle physiology which we were discussing a while ago. Also, it was learned by perfusion of the liver that the amino acids can form sugar. In recent years this type of experiment has been used in the attempt to show that fats passed through the liver will yield sugar. One such set of experiments performed in Dale's laboratory in London, purported to show that when ordinary defibrinated blood was passed through the liver of a dog or cat whose liver glycogen had been reduced to a minimum by feeding the animal for several weeks on a high fat diet, more sugar came out of the liver than could be accounted for by the small amount of glycogen remaining or by the protein metabolism of the liver. The inference was that the excess sugar was coming from fat. These experiments published by Burn and Marks (18) were repeated in our laboratory by Dr. Gregg (19) with more careful attention to several details than Burn and Marks had applied to the experiments. For example, Burn and Marks claimed that the dis-

tribution of glycogen remaining in such a liver was perfectly uniform from lobe to lobe. Gregg found that this was not the case. Secondly, they overlooked the fact that much of the reducing substance of the blood is not sugar at all, but is uric acid, creatinine, glutathione, ergothionine, etc. In other words, they failed to determine the true or fermentable sugar. Gregg supplied this defect and he found that the true sugar coming from the liver not only did not increase, but actually decreased in a considerable majority of his experiments. It was necessary, Gregg found, to set up real carbohydrate and fat balances from the beginning to the end of the experiment. Such balances are illustrated in the accompanying table (Table I).

TABLE I.

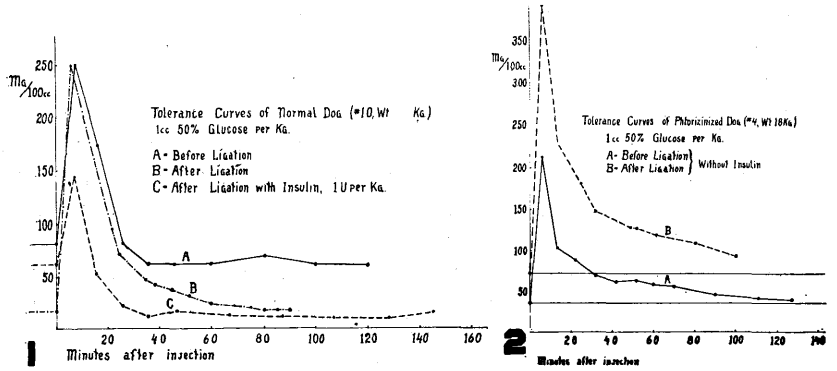
CARBOHYDRATE AND FAT BALANCE IN LIVER PERFUSION.

TOTAL WEIGHTS	BEGINNING		END	
	Carboh. gm.	Lipids gm.	Carboh. gm.	Lipids gm.
Blood sugar	0.644	.....	0.568	.....
Blood sugar removed	.....	.....	0.246	.....
Free sugar	0.206	.....	0.050	.....
Glycogen as free sugar	0.330	.....	0.183	.....
Liver lipids	.....	4.740	.....	3.670
Blood lipids	.....	0.567	.....	0.400
Blood lipids removed	.....	.....	.....	0.189
Total grams	1.180	5.307	1.047	4.259

More recently Jost (20) has claimed that perfusion of the liver with phospholipids yields sugar which can only be accounted for on the assumption that these phospholipids are converted over to carbohydrate. I have no means of judging the accuracy of this work. However, some other experiments reported from Best's laboratory in Toronto, which claim to prove that lecithin fed to diabetic animals causes the production of extra sugar in the urine, have been checked in our laboratory in a few experiments and have been found incorrect. When carefully purified lecithin is fed to a diabetic animal, it does not affect the D:N ratio or the R. Q. It is quite possible that this type of experiment will eventually furnish convincing evidence that sugar may be produced from fat. In our laboratory Dr. Eaton and I have found that a fraction of the fat extractable from the

pancreas and belonging to the cerebrosides (or possibly sphyngomyeline), depresses the R. Q. and increases the D:N ratio of depancreatized dogs (21).

The change in sugar tolerance when an animal is made diabetic with phlorhizin is shown in Charts 1 and 2, taken from a recent publication on this subject from the Rochester laboratory (4). When a certain definite doze of glucose was injected into a vein of a normal dog and a sample of blood drawn from another vein at frequent intervals, "tolerance curves" like those in Chart 1 were obtained. These could be repeated at three-hour intervals. When insulin was given with the glucose a lower curve (higher tolerance) was obtained (curve C). In the phlorhizinized dog (Chart 2) the tolerance



curve from the same dose of glucose per kilogram of body weight gave a lower curve (A). This does not indicate higher tolerance; it only shows that some of the sugar passed out through the kidney. When the kidney blood vessels were ligated so that no sugar could escape from the blood to the urine, the dose of glucose produced a much higher curve. The lower tolerance of the diabetic organism is shown by the difference between this curve and a similar test (after ligation of the vessels) in the normal dog (Chart 1). The lower tolerance of the phlorhizinized dog is shown especially by the prolongation of curves A and B in Chart 2 and is due probably to injury to vessels of the liver, similar to the injury produced in the kidney.

The study of the respiratory metabolism of diabetic animals has in the main confirmed the study of D:N ratios. The verdict to date has been that there is no diminution of the R. Q. to the point where one could safely infer that sugar is being

formed from fat. I know of only a few experiments, including one from Boothby's laboratory, which furnished R. Q.'s too low to be accounted for on any other hypothesis. Wilder, Boothby and Beeler (22) were studying quite exhaustively a single case, and they were testing out the specific dynamic action of high fat meals on the diabetic subject. In a few instances they obtained quotients immediately following the meal as low as 0.62 or 0.61. The quotients gradually rose from that level to the level prevailing before the meal, namely, about 0.69. Boothby did not comment on the significance of this quotient in reporting the work. Likewise in Joslin's laboratory in a few cases out of a large number which he studied following meals containing a considerable amount of fat, quotients as low as 0.57, 0.58 and 0.62 were found. Joslin believed these quotients were really significant of gluconeogenesis from fat. Magnus-Levy has stated that in diabetes a quotient as low as 0.65 cannot be explained in any other way and he says a quotient of 0.60 would prove it beyond peradventure. But such a quotient would be obtained in the diabetic only if in the metabolism of 200 grams of protein and 250 grams of fat 350 grams of sugar were formed besides 40 grams of Beta-hydroxybutyric acid.

The main difficulty which stands in the way of getting crucial evidence concerning the conversion of fat to carbohydrate by the R. Q. method is that, if combustion of carbohydrate keeps up with its formation, there is no lowering of the R. Q. For example, if the palmitic acid should be converted to glucose with an R. Q. of 0.60, as described above (page 342), and should then be immediately burned with an R. Q. of 1.0 the quotient obtained would be somewhere between these two values and the low R. Q. would entirely disappear. It occurred to us that the fatty seeds during germination, where low R. Q.'s have frequently been reported and have been interpreted to mean that the fat is being converted to sugar for later conversion to cellulose or combustion would be suitable objects in which to separate the two processes: (1) conversion of the fat to carbohydrate and (2) the combustion of the carbohydrate. The castor bean was chosen and its respiratory metabolism at various stages during germination was studied in the so-called Warburg respirometer (23). It was soon found in confirmation of earlier work on this seed, that after the first few hours of germination low R. Q.'s are regularly obtained.

The table shows some of these quotients obtained on individual beans (Table II). It will be observed that the level of the quotients depends to some extent upon the stage of growth reached. The next question was to study on the whole young plant separated from the endosperm of the seed and to compare its respiratory metabolism with that of the whole germinating bean. The next table shows that the bean as a whole gives as usual its low R. Q., but that when the cotyledons are separated out of the bean and together with the hypocotyl or radicle are

TABLE II.

CASTOR BEAN EXPERIMENTS.

Single Bean in Warburg App.
Variation with Stage.

Bean No.	Stage of growth L.of hypocotyl mm.	Length of exper. min.	RESP. EXCH.		R. Q.
			CO_2 cu. mm.	O_2 cu. mm.	
13.....	12	69.0	234.9	345.6	0.679
14.....	12+	46.5	155.8	231.4	0.535
17 (1).....	16	30.0	208.2	337.8	0.617
18 (2).....	16	32.0	211.4	407.8	0.518
16 (1).....	19	32.0	142.6	247.6	0.576
16 (2).....	19	32.0	130.0	223.3	0.582
					Av.0.585
18.....	20	15.0	83.4	252.9	0.337
12 (1).....	23	34.5	117.3	406.3	0.289
12 (2).....	23	23.0	107.8	287.4	0.373
12 (3).....	23	22.5	98.0	320.4	0.306
10.....	24	31.5	146.7	413.8	0.355
11.....	29	32.5	127.9	496.9	0.257
19.....	32	41.0	160.6	420.9	0.382
20.....	33	37.5	184.0	481.2	0.382
			Av.20-33 mm		0.323

studied in the respirometer, quotients approaching those for combustion of carbohydrate alone are obtained. (Table III.) Comparing now the respiratory metabolism of the endosperm by itself with that of the whole bean, we find that its R. Q. instead of being slightly lower as we expected, is slightly higher. This is probably due to the fact that it is necessary to strip off the seed coat and thereby to expose the endosperm tissue more completely to the outside air, and this results in combustion of some of the already formed carbohydrate. Comparing these two, however, with that of the whole plant, we

find the same contrast as before. Finally, we studied the respiratory metabolism of a considerable number of beans by confining them for several days in a glass bottle and analyzing the air contained in the bottle at the termination of this period. From such studies we learned that the low R. Q.'s prevail not merely over the few minutes necessary to obtain the R. Q. on the individual seed, but throughout the entire germination period. We have here then a demonstration that the two processes can be studied separately—the conversion of fat to sugar producing a low quotient, and the young plant then oxidizing a portion of this sugar and giving a high quotient.

TABLE III.

RESPIRATORY EXCHANGE OF WHOLE BEAN, ENDOSPERM AND NEW PLANT.

No.	Part	Stage	Length of exper., min.	CO_2 cu. mm.	O_2 cu. mm.	R. Q.
32	Whole bean	40 mm., 1 branch	59.5	236.2	612.2	0.386
32	Endosperm	40 mm., 1 branch	52.0	195.9	426.8	0.459
32	New plant	40 mm., 1 branch	72.0	155.8	140.8	1.106
33	Whole bean	45 mm., 4 branches	57.0	292.9	604.5	0.484
33	Endosperm	45 mm., 4 branches	44.5	184.0	331.7	0.555
33	New plant	45 mm., 4 branches	70.0	173.3	192.5	0.90

The conversion of fat to carbohydrate in these beans has been confirmed by two other methods. Chemical analyses which Dr. H. B. Pierce has carried out in our laboratory demonstrate that the percentage of fat steadily falls from the time germination begins to the end, that the percentage of protein scarcely changes at all, but that the percentage of sugar identified as cane sugar, increases, as does also the percentage of crude fiber or cellulose. The other method consists of burning the entire bean at different stages in a modified oxy-calorimeter. This instrument was devised by Benedict and Fox at Boston for the purpose of studying the heat value of mixtures of food-stuffs when burned in pure oxygen. This was modified sufficiently to collect and weigh the CO_2 formed, to keep the temperature down by cooling the air, and by using a more accurate spirometer so as to measure the oxygen consumed. Dr. Daggs in our laboratory has used this apparatus to burn the ungerminated bean and the bean germinating at several distinct stages up to a total length of the hypocotyl of about

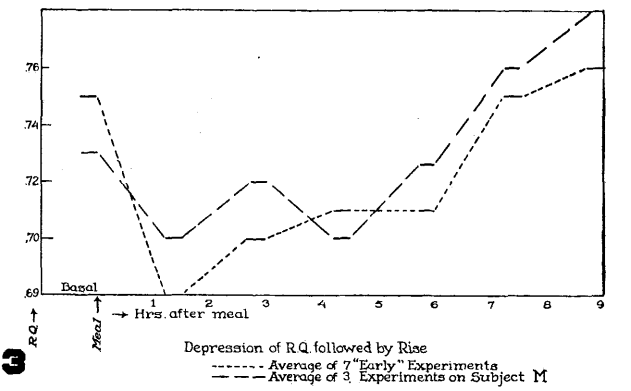
3 inches. The R. Q. increases steadily from the ungerminated stage up to the last stage studied (24).

We have thus obtained a complete demonstration of the conversion of fat to carbohydrate and the partial oxidation of the carbohydrate with the characteristic effects on the respiratory metabolism.

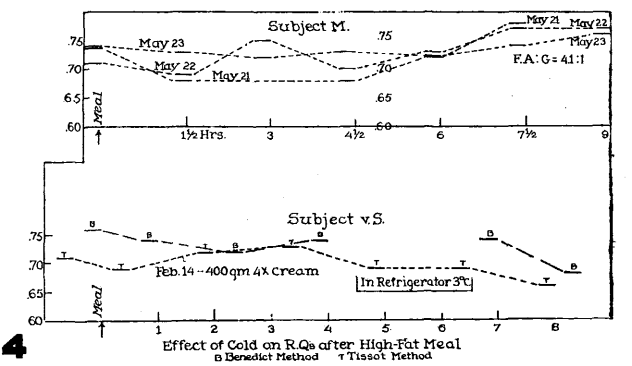
With Drs. Estelle E. Hawley and Carroll M. Johnston (25) we have studied the problem in human subjects. It happened that one of them had an unusually high tolerance for fat. It occurred to us that in such an individual by prolonging a tolerably high fat diet we might deprive him of glycogen sufficiently so that when he was given a large meal of butterfat, selected because it is already emulsified in the form of cream, and therefore quickly digested, the earlier quotients after the meal would show a considerable depression of the quotient, signifying conversion of some of the fat to sugar and its storage as glycogen. Later this glycogen would be mobilized and burned and as a consequence the R. Q. would rise. This hypothesis was predicated on two other demonstrated facts: (1) That at best it is difficult to convert fat to carbohydrate, and (2) that the demand for glycogen as tissue reserve at times dominates the demand for sugar as fuel. Hence to exhibit the conversion it would be necessary to establish these special conditions: (1) Just that degree of tissue hunger for glycogen which would cause retention of any sugar formed; (2) that there should be no other adequate source of sugar available, and (3) that the subject at the moment of test would be already accustomed to digesting and absorbing large amounts of fat. With these conditions rightly adjusted, the hypothesis was that a certain sequence of R. Q.'s would be obtained that could not be plausibly explained in any other way. The low quotient immediately following a high fat meal when averaged with the high quotient later in the day, would produce a quotient which would stand near the accepted level for combustion of the ingested fat.

Dr. Gregg, in our laboratory, had calculated that the theoretical quotients for butter fat should be 0.72, instead of the usually accepted 0.707 for mixed food or body fats, the higher level being explained by the presence of lower fatty acids in butter which give higher quotients than the usual food fats. Encouragement was obtained from the earlier experiments on this subject and then other subjects, to a total number

of seven, were studied on the same high fat diet. The last diet consisted exclusively of 4X cream, actually 37½ per cent fat by analysis. Only this diet of cream gave the best results (from our point of view. The charts 3 and 4 show that the predicted sequence of quotients could be obtained in single experiments or as an average of several experiments on the same subject or several experiments on different subjects. They are best



3 Depression of R.Q. followed by Rise
------ Average of 7 "Early" Experiments
— — — Average of 3 Experiments on Subject M



4 Effect of Cold on R.Qs after High-Fat Meal
B Benedict Method T Tissot Method

obtained, however, while the subject is still somewhat unaccustomed to the high fat diet. This was not anticipated. The phenomenon of adaptation or improved tolerance to high fat diet has only been observed so far as we are aware by Wigglesworth (26), who observed it in rats. It shows up clearly at several points in our experiments.

The best results, from the standpoint of the hypothesis, were obtained before this improved tolerance had asserted itself. One of the charts shows the improving tolerance in

three successive days on the same subject (M). We call attention to the fact also that sometimes these low quotients continue throughout the day, more especially in subject H, who had a very low tolerance for fat, both in the sense of being unable to oxidize the fat successfully and in the sense of showing the highest ketosis of any of the subjects. In the attempt to explain these low R. Q.'s we have calculated the theoretical depression of the quotient which might conceivably be produced by conversion of protein to sugar. The method involves a rather long calculation which I shall not have time to give in detail. It is a well-established method first introduced by Magnus-Levy and used subsequently by Lusk, Geelmuyden, Macleod, and others. In our experiment if we assume that 58 per cent of the protein metabolized were converted to sugar and stored as glycogen, there would be as a maximum a reduction of the quotient, amounting to 0.025. Secondly, we have undertaken to determine how much the quotient might be lowered by conversion of the glycerol of fat to sugar. It is well known that in the diabetic organism when glycerol is fed, extra sugar appears in the urine equivalent to the amount of sugar which can be formed if all of the carbon of the glycerol were converted to glucose. Making this calculation in our experiments we found that if all the glycerol of the fat meal were converted to sugar, and stored as glycogen, the quotient might be depressed as much as 0.03 and we have some experiments in which the theoretical amount of glycerol was fed on one of the days adjacent to the all cream diet. There was at times a similar drop in R. Q.'s immediately after the meal following glycerol as following the high fat, which would lead one to think that on the day of high fat ingestion all of the glycerol separated from the fatty acids and was converted to glycogen. It is perfectly easy to imagine that this happens when nothing but glycerol is fed, but the total amount of glycerol of the fat cannot possibly be separated from the fatty acid after absorption into the circulation unless the fatty acids at the same time were metabolized. Hence we are limited in calculating the glycerol available for conversion to sugar and thence to glycogen to that amount which corresponds to the highest fat metabolism of the hour when the R. Q. was determined. The highest fat metabolism in a single hour in any of these experiments was 10 grams of the butter fat. The glycerol is roughly one-tenth of this, or one gram. Conversion

of one gram of glycerol to glucose would not lower the quotient more than 0.003.

Next we attempted to correlate the R. Q.'s with the ketosis developed in these subjects. The acetone bodies were determined in the blood and also in the urine. If the ketosis were responsible for the low R. Q.'s as Shaffer has demonstrated should be the case from his *in vitro* work, the quotients should be lowest when the ketosis is highest, and *vice versa*. Our series show, however, that this is not the case whether we consider the total acetone of the blood or of the urine. Finally, we have calculated what would be the effect on the R. Q. from the increase in the ketone bodies in the blood from one period to the next.

It is necessary also to make allowance for the increased ammonia production which results from the acidosis. Making these calculations in several of our typical experiments, we found that the only effect is a lowering of the quotient of not more than 0.01. Now if we imagine that all of these various influences known to have the effect of lowering the R. Q. were operative at once, which in itself is very improbable, we might have a total effect of about 0.04. In other words, a quotient which would be about 0.73, if the fat were oxidized completely as fast as it was absorbed, would be depressed by these several factors to a level not lower than about 0.69. This is the familiar R. Q. of total diabetes.

In this work we have literally scores of quotients lower than this. A considerable number in the neighborhood of 0.60 to 0.65, still more from 0.65 to 0.69. As we have said before, these quotients below 0.69 occur most frequently in the person with a low tolerance or in the very early experiments on other subjects which had a normal or high tolerance for fat.

There is one other possible explanation of low quotients which should be considered before we infer that we have demonstrated in these experiments the formation of sugar from fat. You will remember that the most plausible theory for the oxidation of fatty chains in the body is Knoop's theory of Beta-oxidation. Suppose we have a fatty acid like oleic acid with 18 carbons, and with a double bond between the 9th and 10th carbon. It is assumed that the chain first breaks at this weak point in the double bond and two chains of 9 carbons each are obtained which may be oxidized at either end. Now, if we try to imagine an orderly process of Beta-oxidation, that is, splitting off of two carbons at a time with subsequent formation of CO_2

and water by way of several intermediary products, it is clearly possible that the absorption of oxygen may considerably outrun the formation of CO_2. We believe it is necessary to rule out this possibility before concluding that in the human subject, on a high cream diet, the conversion of fat to carbohydrate has been demonstrated. Furthermore, it will be necessary to find the carbohydrate.

LITERATURE CITED.

(1) **Carman, J. S., Smith, H. G., Havens, Gladys C. and Murlin, J. R.** The Nutritive Value of Cereal Breakfast Foods. II. Digestibility in vitro with a study of methods. Jour. Nutr., 1929, II, 91.

(2) **Ferris, S. J., and Lusk, G.** The Gastric Inversion of Cane Sugar by Hydrochloric Acid. Amer. Jour. Physiol., 1898, I, 277.

(3) **Pierce, H. B., Nasset, E. S., and Murlin, John R.** Studies on the Transplanted Intestinal Loop. II. A Humoral Influence in the Secretion of Intestinal Juice. Jour. Biol. Chem., 1932, XCVII, xlii.

(4) **Goldstein, L. A., Tatelbaum, A. J., Ehre, S., and Murlin, J. R.** Glucose Tolerance in the Phlorhizinized Dog as Affected by Renal Vessel Ligation and by Insulin. Amer. Jour. Physiol., 1932, CI, 166.

(5) **Ringer, A. I., and Baumann, E. J.** Carbohydrates and their Metabolism. Endocrinology and Metabolism. New York, 1922, III, 252.

(6) **Hill, A. V.** The Heat Production of Surviving Amphibian Muscles During Rest, Activity and Rigor. Jour. Physiol., 1912, XLIV, 466. (See for full bibliography, A. V. Hill, Muscular Activity, Baltimore, 1922.)

(7) **Meyerhof, O.** Zur Verbrennung der Milchsäure in der Erholungsperiode das Muskels, Pflügers Arch. 1919, CLXXV, 88. (See also Meyerhof, O., Chemical Dynamics of Life Phenomena, Philadelphia, 1924.)

(8) **Hill, A. V.** The Revolution in Muscle Physiology. Physiol. Rev., 1932, xii, 56.

(9) **Eggleton, P., and Eggleton, C. P.** The Inorganic Phosphate and a Labile Form of Organic Phosphate in the Gastrocnemius of the Frog. Biochem. Jour. 1927, XXI, 190.

(10) **Fiske, C. H., and Subarrow, Y.** Science, 1927, LXV, 401.

(11) **Lundsgaard, E.** Untersuchingen über Muskelkontractionen ohne Milchsäurebildung, Biochem. Zeitschr. 1930, XXXVII, 162.

(12) **Fischer, E.** Die Wärmebildung des Skeletmuskels bei aufgehobener Milchsäurebildung, Pflüger's Arch., 1931, CCXXVI, 500.

(13) **Lundsgaard, E.** Uber die Energetik der anaeroben Muskelkontraction, Biochem. Zeitschr., 1931, 233, 322.

(14) **Lohmann, K.** Chemische Natur des Koferments der Muskelsäurebildung. Biochem. Zeitschr., 1931, 237, 445.

(15) **Cori, C. F., and Cori, G. T.** The Fate of Sugar in the Animal Body. II. The Relation Between Sugar Oxidation and Glycogen Formation in Normal and Insulinized Rats During the Absorption of Glucose. Jour. Biol. Chem., 1926, LXX, 557.

(16) **Zuelzer, G.** Untersuchungen über den experimentellen Diabetes, Berl. Klin. Woch., 1907, 474.

(17) **Colwell, A. R., and Bright, E. M.** Suppression of Glucose Combustion by Continuous Prolonged Epinephrin Administration. Amer. Jour. Physiol., 1930, XCII, 555.

(18) **Burn, J. H., and Marks, H. P.** The Production of Sugar in the Perfused Liver from Non-protein Sources. Jour. Physiol., 1926, LXI, 497.

(19) **Gregg, D. E.** The Relation of Carbohydrates and Lipids in the Perfused Liver. Amer. Jour. Physiol., 1933, CIII, 79.

(20) **Jost, H.** Uber bie Umwandlung von Fett in Kohlehydrat. I. Über die Phosphatide als Vorstufen der Fettoxydation. Zeitschr. physiol. Chem., 1931, CXCVII, 90.

(20a). **Best, C. H., and Hershey, J. M.** Further Observations on the Effects of Some Component of Crude Lecithin on Depancreatized Animals. Jour. Physiol., 1932, LXXV, 49.
(21) **Eaton, A. G., and Murlin, J. R.** Influence of a certain fraction of Pancreas Lipids on Carbohydrate Metabolism of Depancreatized Dogs. Proc. Soc. Exp. Biol. and Med., 1933, XXXI, No. 1.
(22) **Wilder, R. M., Boothby, W. M., and Beeler, C.** Studies on the Metabolism of Diabetes. Jour. Biol. Chem., 1922, LI, 311.
(23) **Murlin, John R.** Respiratory Metabolism of the Germinating Castor Bean. Proc. Soc. Exp. Biol. and Med., 1932, XXIX, 407.
(24) **Daggs, R. G., and Wardlaw, H. C. H.** A Study of the Conversion of Fat to Carbohydrate in the Germinated Castor Bean by Means of a Modified Oxycalorimeter. Proc. Amer. Physiol. Soc., Amer. Jour. Physiol., 1932, CI, 27.
(25) **Hawley, E. E., Johnston, C. M., and Murlin, J. R.** The Effects of High Fat Diets on Respiratory Metabolism and Ketosis. Proc. Amer. Physiol. Soc., Amer. Jour. Physiol., 1933, CV, 46; Jour. Nutr., 1933, VI, No. 6.
(26) **Wigglesworth, V. B.** Studies on Ketosis. I. The Relation between Alkalosis and Ketosis. Biochem. Jour., 1924, XVIII, 1203.

Frontiers of Medicine.

One of the Century of Progress Series, this book delves much farther back into history than the last century for its background. With deft sure strokes the history of medicine is drawn, a picture which merges into the dynamic medical frontiers of today, where disease and the threat of disease are attacked on innumerable specialized sectors. The middle chapters give the impression of being hurriedly written, but the final chapters round out to an excellent discussion of present achievements and future possibilities.—L. H. S.

Frontiers of Medicine, by Morris Fishbein. x+207 pp. Baltimore, the Williams and Wilkins Co. 1933.

Telling the World.

Perhaps nothing in this "Century of Progress" has been more striking than the development of communication. Telegraph, telephone, wireless, radio—the story of all of these is unfolded graphically by the former Chief Signal Officer of the U. S. Army. The opportunity is embraced to familiarize the reader with the part played by the Signal Corps in the advances in this great field. A new terminology is developed and defined. The Century of Progress Series appears to be sustaining the high standard set by the earlier volumes.—L. H. S.

Telling the World, by Gen. George O. Squier. xii+163 pp. Baltimore, the Williams and Wilkins Co. 1933.

Fighting the Insects.

This is a most interesting story of the life, experiences, contacts, unusual situations, extensive travels and everyday duties of the author, an outstanding entomologist. Woven into this life story is the history of the development of many phases of economic entomology as they have been seen personally by a big man in a very prominent administrative position. The problems are made real and intensely interesting by the personal experiences and contacts of Dr. Howard as he is fighting the insects through his research workers in the Bureau of Entomology.—D. M. DeLong.

Fighting the Insects, by L. O. Howard. 233 pp. New York, The MacMillan Co. 1933.